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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/504,280	02/15/2000	Mike A. Clark	phoe-0057	5368

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Woodcock Washburn Kurtz
Mackiewicz & Norris LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103

EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/504,280	CLARK, MIKE A.	
	Examin r	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14-17 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14-17 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-8,14-17 and 24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/22/2004 has been entered.

Claims 1-8, 14-17, 24 are pending. Applicant's election with traverse of group II and the species succinimidyl succinate in Paper No. 7 is acknowledged. Applicant timely traversed the restriction (election) requirement in Paper No. 7. Claims 1-8, 14-17, 24 are being examined to the extent that they read upon the elected invention and/or species.

Applicant's arguments have been fully considered but they are moot because they are directed to rejections have either been overcome or withdrawn.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 14-17, 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Rhee (A) as evidenced by Hudziak (U. S. Patent No. 5677171).

Rhee discloses medical articles in the form of extruded elongated hollow cylinders or tubes. The composition used to form a tube is a pharmaceutically acceptable non-immunogenic composition formed by covalently binding atelopeptide collagen to pharmaceutically pure, synthetic, hydrophilic polymers via specific types of chemical bonds to provide collagen/polymer conjugates. Column 4, lines 15-23. The synthetic hydrophilic polymer may be polyethylene glycol and derivatives thereof having a weight average molecular weight over a range of from about 100 to about 20,000. The compositions may include other components such as biologically active proteins such as cytokines which may be incorporated in the tubes. Column 4, lines 30-36. Presently preferred hydrophilic polymers are mono-, di-, and multifunctional polyethylene glycols (PEG). Column 6, lines 58-62. Difunctional PEG preferably has a molecular weight of about 400 to about 40,000. Column 6, lines 66-67. Polyfunctional molecules are capable of crosslinking the compositions of the invention, and may be used to attach cytokines or growth factors to collagen which can diffuse out of the tubes. Column 7, lines 12-15. The cytokines and growth factors can either be admixed with the collagen-polymer conjugate or chemically coupled to the conjugate. For example, one may incorporate tumor necrosis factor (TNF). Column 8, lines 22-28; column 31, claim 6. One may chemically link the cytokines and growth factors to the collagen-polymer composition by employing a suitable amount of multifunctional polymer molecules during synthesis. The cytokines may then be attached to the free polymer ends by the same method used to attach PEG to collagen, or by any other suitable method. Column 8, lines 43-49.

Accordingly, Rhee discloses TNF covalently bound to PEG molecules having an approximate weight average molecular weight in the range of about 100 to about 40,000 and a method of doing same. Conjugates with ester linkages are made by reacting the polymer succinimidyl ester with free amino groups present on collagen (lysine residues) to form a collagen-PEG conjugate. Paragraph bridging columns 19-20. Accordingly, the "PEG is covalently bound to primary amine groups on" TNF. To form the conjugates used to make the tubes collagen must be chemically bound to a synthetic hydrophilic polymer. This can be carried out in a variety of ways. In accordance with the preferred method, the synthetic hydrophilic polymer is activated and then reacted with the collagen. Column 13, lines 39-44. Since the conjugates are to be used in the human body it is important that all of the components, including the polymer, collagen, and linking group, if used form a conjugate that is unlikely to be rejected by the body. Column 13, lines 54-58. Accordingly, the linkers are "biocompatible." The first step in forming the collagen-polymer conjugates generally involves the functionalization of the PEG molecule. Column 14, lines 9-11. One form of activated PEG which has been found to be particularly useful in connection with the present invention is mPEG-succinate-N-hydroxysuccinimide ester (SS-PEG). Column 14, lines 46-50. Preferably, the cytokine is first reacted with a molar excess of dPEG*. Column 20, lines 35-36. One may administer antiviral and antitumor factors such as TNF, interferons, CSFs, TGF-β, and the like for their pharmaceutical activities. Column 21, lines 44-46. The present specification teaches that suitable biocompatible linking groups include succinimidyl succinate (SS) (page 7, lines 13-16). The mPEG-succinate-N-hydroxysuccinimide ester (SS-PEG) disclosed by Rhee (column 14, lines 46-50) appears to entirely consistent with

succinimidyl succinate biocompatible linker of the present claims. Although Rhee does not disclose that TNF "comprises the ability to kill METH A tumors in vivo," no difference is seen between the TNF disclosed by Rhee and the "a polypeptide having TNF biological activity" of the present claims. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, the properties applicant discloses and/or claims, i.e., "the ability to kill METH A tumors in vivo," are necessarily present in Rhee's TNF. It is noted that Hudziak (U. S. Patent No. 5677171) discloses that both TNFα and TNFβ induce of hemorrhagic necrosis of Meth A sarcomas in vivo (column 1, full paragraph 4).

Claim Rejections - 35 USC § 103

Claims 1, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee (A) in view of Tsutsumi (AL, cited by Applicants).

Rhee discloses medical articles in the form of extruded elongated hollow cylinders or tubes. The composition used to form a tube is a pharmaceutically acceptable non-immunogenic composition formed by covalently binding atelopeptide collagen to pharmaceutically pure, synthetic, hydrophilic polymers via specific types of chemical bonds to provide collagen/polymer conjugates. Column 4, lines 15-23. The synthetic hydrophilic polymer may be polyethylene glycol and derivatives thereof having a weight average molecular weight over a range of from about 100 to about 20,000. The compositions may include other components such as biologically active proteins such as cytokines which may be incorporated in the tubes. Column 4, lines 30-36. Presently preferred hydrophilic polymers are mono-, di-, and multifunctional polyethylene glycols

(PEG). Column 6, lines 58-62. Difunctional PEG preferably has a molecular weight of about 400 to about 40,000. Column 6, lines 66-67. Polyfunctional molecules are capable of crosslinking the compositions of the invention, and may be used to attach cytokines or growth factors to collagen which can diffuse out of the tubes. Column 7, lines 12-15. The cytokines and growth factors can either be admixed with the collagen-polymer conjugate or chemically coupled to the conjugate. For example, one may incorporate tumor necrosis factor (TNF). Column 8, lines 22-28; column 31, claim 6. One may chemically link the cytokines and growth factors to the collagen-polymer composition by employing a suitable amount of multifunctional polymer molecules during synthesis. The cytokines may then be attached to the free polymer ends by the same method used to attach PEG to collagen, or by any other suitable method. Column 8, lines 43-49. Accordingly, Rhee discloses TNF covalently bound to PEG molecules having an approximate weight average molecular weight in the range of about 100 to about 40,000 and a method of doing same. Conjugates with ester linkages are made by reacting the polymer succinimidyl ester with free amino groups present on collagen (lysine residues) to form a collagen-PEG conjugate. Paragraph bridging columns 19-20. Accordingly, the "PEG is covalently bound to primary amine groups on" TNF. To form the conjugates used to make the tubes collagen must be chemically bound to a synthetic hydrophilic polymer. This can be carried out in a variety of ways. In accordance with the preferred method, the synthetic hydrophilic polymer is activated and then reacted with the collagen. Column 13, lines 39-44. Since the conjugates are to be used in the human body it is important that all of the components, including the polymer, collagen, and linking group, if used form a conjugate that is unlikely to be rejected by the body. Column 13, lines 54-

58. Accordingly, the linkers are "biocompatible." The first step in forming the collagen-polymer conjugates generally involves the functionalization of the PEG molecule. Column 14, lines 9-11. One form of activated PEG which has been found to be particularly useful in connection with the present invention is mPEG-succinate-N-hydroxysuccinimide ester (SS-PEG). Column 14, lines 46-50. Preferably, the cytokine is first reacted with a molar excess of dPEG*. Column 20, lines 35-36. One may administer antiviral and antitumor factors such as TNF, interferons, CSFs, TGF-β, and the like for their pharmaceutical activities. Column 21, lines 44-46. The present specification teaches that suitable biocompatible linking groups include succinimidyl succinate (SS) (page 7, lines 13-16). The mPEG-succinate-N-hydroxysuccinimide ester (SS-PEG) disclosed by Rhee (column 14, lines 46-50) appears to entirely consistent with succinimidyl succinate biocompatible linker of the present claims. Although Rhee does not disclose that TNF "comprises the ability to kill METH A tumors in vivo," no difference is seen between the TNF disclosed by Rhee and the "a polypeptide having TNF biological activity" of the present claims. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, the properties applicant discloses and/or claims, i.e., "the ability to kill METH A tumors in vivo," are necessarily present in Rhee's TNF. Rhee does not expressly state that the TNF is human TNFα.

Tsutsumi discloses that TNFα is a promising new therapeutic agent with anti-tumor effects (page 9, left column, full paragraph). Tsutsumi also discloses natural human TNFα (Abstract). The limitation "recombinant" in the present claims is a product-by-process limitation. Although Tsutsumi does not describe the recombinant

production of TNF-α, the recitation of "recombinant" does not positively limit the TNF-α in the present claims absent a showing that the "recombinant" process imparts a novel or unexpected property to the TNF-α, as it is assumed that equivalent products are obtainable by multiple routes. The burden is upon the applicants to establish a patentable distinction between Tsutsumi's TNF-α and "recombinant" TNF-α. Tsutsumi does not teach, in the sense that Tsutsumi does not anticipate, the attachment of human TNFα to PEG molecules having an approximate weight average molecular weight of 20,000.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to attach TNF to PEG molecules having an approximate weight average molecular weight of 20,000, as taught by Rhee, and to modify that teaching by using human TNFα, as taught by Tsutsumi, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because TNFα is a promising new therapeutic agent with anti-tumor effects. The invention is prima facie obvious over the prior art.

Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee (A) in view of Tsutsumi (AL, cited by Applicants) as applied to claim 1 above and further in view of Mark (V).

Rhee in view of Tsutsumi teach the attachment of human TNFα to PEG molecules having an approximate weight average molecular weight of 20,000. Rhee in view of Tsutsumi do not teach human TNF mutated by deleting amino acids 1-9 of the mature TNF protein.

Mark teaches that human TNF mutated by deleting amino acids 1-9 of the mature TNF protein has the same biological activity as mature TNF (page 413, Table II). Mark does not teach the attachment of human TNFα to PEG molecules having an approximate weight average molecular weight of 20,000.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to attach human TNFα to PEG molecules having an approximate weight average molecular weight of 20,000, as taught by Rhee in view of Tsutsumi, and to modify that teaching by using human TNF mutated by deleting amino acids 1-9 of the mature TNF protein, as taught by Mark, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because a smaller peptide with the same biological activity of a larger peptide would require a smaller net amount on a mole per mole basis for administration. The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

Claims 1-4, 14-17, 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass "a polypeptide having TNF biologic activity" "wherein said biological activity of said polypeptide comprises the ability to kill METH A tumors in vivo." Accordingly, the claims are directed to or encompass a genus

of polypeptides having TNF biological activity. However, no common structural attributes identify the members of the genus. The claims do not indicate what distinguishing structural attributes are shared by the members of the genus. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted.

Vas-Cath Inc. v. Mahurkar , 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

With the exception of tumor necrosis factor, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were

found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, the full breadth of the claims fails the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

Limiting the claims "modified TNF, comprising TNF ... wherein said TNF kills METH A tumors in vivo" would adequately describe the TNF of the claimed invention and would not raise an issue under 35 U.S.C. § 112, second paragraph.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

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FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JANUARY 9, 2005